REMARKS

Applicant respectfully requests reconsideration. Claims 52-77 were previously pending in this application. Claims 54, 60 and 64 have been amended. No new matter has been added.

Objection under 37 CFR 1.75(c)

Claim 64 is objected to under 37 CFR 1.75(c) as being of improper dependent form. Applicant has amended claim 64 to recite that the composition is formulated for intravenous or intraperitoneal administration. Support for this amendment can be found on page 22, lines 9-15.

Reconsideration and withdrawal of this objection is respectfully requested.

Rejection under 35 U.S.C. §112

Written Description

Claim 54 is rejected under 35 U.S.C. §112, first paragraph, written description. According to the Examiner, the phrase "wherein the CpG is not part of a palindromic sequence" is a new subgenus that is not supported by the specification and thus is new matter.

Claim 54 has been amended to recite that the palindromic sequence is a 6 base palindromic sequence.

The specification describes the "subgenus" of immunostimulatory oligonucleotides having a CG dinucleotide that is not part of a 6 base palindromic sequence. See for example page 13, lines 36-38. One of ordinary skill in the art would understand the structural features shared by members of this "subgenus" and could readily identify species of the genus. In addition, the specification provides various species of this "subgenus" including ODN 1, 1c, 1d, 2, 3D, 3Da, 3dB, 3De, 3Dg, 3M, 3Md, and 3Me). See pages 14 and 15, Table 1. Thus, one of ordinary skill in the art would appreciate that Applicant was in possession of the claimed "subgenus" in view of the specification.

Reconsideration and withdrawal of this rejection is respectfully requested.

Enablement

Claim 54 is rejected under 35 U.S.C. § 112, first paragraph, enablement. According to the Examiner, the specification does not enable a composition wherein the CpG is not part of a palindromic sequence. The Examiner however acknowledges that the specification does enable a composition for activating a non-specific immune response in a subject comprising an immunostimulatory CpG oligonucleotide.

Claim 54 has been amended to recite that the palindromic sequence is a 6 base palindromic sequence.

A claim is enabled if it can be practiced by one of ordinary skill in the art without undue experimentation. Whether the experimentation required to practice an invention is undue is determined by an analysis of various factors including the nature of the invention, the breadth of the claim, the amount of guidance provided by the specification, the state of the art, the level of skill in the art, the level of predictability in the art, the existence of working examples, and the amount of experimentation required to practice the invention. The amount of experimentation required to practice the invention may be large and still not undue if it is the level routinely engaged in by the person of ordinary skill. These factors must be considered in their totality, with no one factor being dispositive. The Examiner has analyzed a number of these factors, and these are discussed below. An analysis of these factors in relation to claim 54 shows that undue experimentation is not required to practice this claim.

Nature of the invention. The invention relates to the discovery of CG containing oligonucleotides having immunostimulatory activity. The specification teaches and demonstrates that the CG dinucleotide need not be present in a 6 base palindrome sequence (as now recited in claim 54) in order to be immunostimulatory. See for example pages 14 and 15, Table 1, ODN 1, 1c, 1d, 2, 3D, 3Da, 3Db, 3De, 3Dg, 3M, 3Mc, 3Md, and 3Me. The Examiner has acknowledged that the specification discloses in vitro and/or in vivo immunostimulation by ODN 1, 1d, 3Db, among others. The Examiner has acknowledged that a composition comprising for example ODN 1, 1d, 3Db, or 3Md is enabled. Applicant notes that all of these oligonucleotides have CG dinucleotides that are not present in a 6 base palindromic sequence.

Breadth of the claim. Claim 54, as now amended, relates to a composition comprising an oligonucleotide delivery complex comprising a lipid or a sterol and a CG containing oligonucleotide having a CG dinucleotide that is not present in a 6 base palindrome sequence. The Examiner states that CG oligonucleotides in which the CG dinucleotide is not present in a palindrome sequence would differ from other CG containing oligonucleotides in terms of accessible targets sites, modes of delivery, formulations, etc. However, the Examiner has not presented any evidence in support of this position. The data in the specification show that many CG containing oligonucleotides can stimulate immune cells whether or not the CG dinucleotide is present in a 6 base palindromic sequence. See for example pages 14 and 15, Table 1, page 16, Table 2, and page 18, Table 3. The immunostimulatory profiles of these oligonucleotides also do not appear to vary according to whether or not the CG dinucleotide is in a 6 base palindromic sequence. See for example page 14 Table 1, ODN 2d versus 3Db.

Applicant also wishes to clarify a statement made the Examiner. The Examiner stated that the CG containing oligonucleotide "functions as an antigen". This is incorrect. The oligonucleotide is immunostimulatory but it is not an antigen. The oligonucleotide does not induce a specific immune response against itself. Rather the oligonucleotide functions by activating immune cells including B cells and NK cells, and stimulating antibody production and induction of cytokines such as IFN-gamma, IL-6, and IL-12.

Amount of guidance provided by the specification. The specification teaches that CG containing oligonucleotides may be present in the context of a palindromic sequence or they may be present in a non-palindromic sequence. See for example page 13 line 19 through to page 15, including Table 1. The guidance provided by the specification relating to the genus of immunostimulatory CG containing oligonucleotides is equally applicable to those oligonucleotides having CG dinucleotides that are not present in a 6 base palindromic sequence. The Examiner has also acknowledged that many of these latter oligonucleotides are immunostimulatory and compositions containing them are enabled (e.g., ODN 1, 1d, 3Db, or 3Md).

State of the art. The Examiner has stated that the art teaches that palindromes must be present in order to effect immune stimulation. However, the Examiner has also readily identified from the specification various oligonucleotides having CG dinucleotides that are not present in 6

base palindromic sequences that are nevertheless immunostimulatory. The invention is premised on the discovery that CG dinucleotides impart immunostimulatory activity. The data show that CG containing oligonucleotides can be immunostimulatory whether or not the CG dinucleotide is present in a 6 base palindromic sequence. Thus the teachings of the specification refute those in the art relating to palindromic sequences.

Working examples. The specification provides a number of working examples that demonstrate immune stimulation by oligonucleotides having CG dinucleotides that are not present in 6 base palindromic sequences. See for example Tables 1, 2 and 4 and pages 14-18. The Examiner has acknowledged these teachings.

In view of these and other Wands factors, one of ordinary skill in the art could practice the claimed invention without undue experimentation.

Reconsideration and withdrawal of this rejection is respectfully requested.

Indefiniteness

Claim 60 is rejected under 35 U.S.C. § 112, second paragraph, in view of the recitation of the term "near". In the interest of expediting prosecution, Applicant has amended the claim to delete this term. Applicant reserves the right to claim this subject matter in a continuing application.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §102

Claims 52-61 and 63-64 are rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent No. 5,723,335 (Hutcherson et al.). Applicant respectfully traverses.

Hutcherson et al. teaches that oligonucleotides having at least one phosphorothiote internucleotide linkage are immunostimulatory by virtue of this backbone modification. Hutcherson et al. does not teach that CG-containing oligonucleotides are immunostimulatory by virtue of the CG dinucleotide.

The Examiner has relied on the teaching in Hutcherson et al. of three specific antisense oligonucleotides that have one or more phosphorothioate internucleotide linkages and that happen to

contain one or more CG dinucleotides (i.e., SEQ ID NO:1, 2 and 3). Hutcherson et al. does not formulate any of these oligonucleotides with liposomes or cationic lipids. See for example col. 10 lines 14-16 which teaches that the buffer control contains sodium acetate and sodium chloride. Therefore Hutcherson et al. does not teach an immunostimulatory CpG containing oligonucleotide associated with a lipid or a sterol, and it therefore does not anticipate the rejected claims.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claim 62 is rejected under 35 U.S.C. §103(a) as being anticipated by U.S. Patent No. 5,723,335 (Hutcherson et al.) in view of U.S. Patent No. 5,703,055 (Felgner). Applicant respectfully traverses.

A prima facie case of obviousness has not been made because there is no motivation to combine the references, no reasonable expectation of success relating to such combination, and the combination does not yield every limitation of the pending claims.

Hutcherson et al. teaches immunostimulatory oligonucleotides having at least one phosphorothioate internucleotide linkage. Hutcherson et al. teaches that it is the presence of the one or more phosphorothioate internucleotide linkages that imparts immunostimulatory activity to the oligonucleotide. When taken as a whole, Hutcherson et al. does not teach that these oligonucleotides must contain a CG dinucleotide in order to be immunostimulatory. Felgner does not teach oligonucleotides that are immunostimulatory by virtue of CG dinucleotide content either. The combination of Hutcherson et al. and Felgner therefore does not yield each and every limitation of claim 62, as the combination does not lead one of ordinary skill in the art to an appreciation of the immunostimulatory capacity of a CG dinucleotide.

In addition, there is no motivation to combine Hutcherson et al. and Felgner at least because the nucleic acids of Hutcherson et al. must comprise at least one phosphorothioate internucleotide linkage and those of Felgner encode proteins. Nucleic acids having phosphorothioate linkages are generally not used to encode proteins because the transcriptional machinery of the cell has evolved to recognize and transcribe naturally occurring DNA (i.e., having a phosphodiester backbone) and not nucleic acids with modified backbones. Rather nucleic acids having phosphorothioate backbone

modifications are more commonly used for example as antisense sequences since the backbone modification functions to promote their stability (and thus increase their half-life). For at least these reasons, one of ordinary skill in the art would not have been motivated and would not have had a reasonable expectation of success of introducing the backbone modifications of Hutcherson et al. into the antigen-encoding nucleic acids of Felgner. For at least these reasons, a *prima facie* case of obviousness has not been made.

Reconsideration and withdrawal of this rejection is respectfully requested.

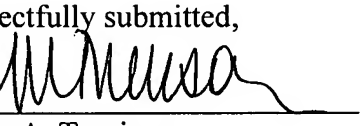
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: September 27, 2007

Respectfully submitted,

By 

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